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Bioterrorism: What All Primary Care Physicians Need to Know

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Editor's Note—*Few natural or intentional threats arouse the concern of emergency management planners in this country more acutely than the use of biological agents as an act of war or terrorism against citizens of the United States. While a vast array of first responders, including elements of the police, fire department, emergency medicine services, and hazardous materials units have been involved in these events, few physicians have been engaged in comprehensive efforts to defend against possible acts of bioterrorism. Particularly in a large-scale covert attack, however, primary care physicians (PCPs) would nonetheless play a front-line role in the detection, evaluation, and response to this threat. Formal educational curricula to inform PCPs about the likely agents of bioterrorism are essential to ensure that cases are identified, reported, treated, and monitored as rapidly and efficiently as possible.*

The Threat of Bioterrorism

Background

Evidence of attempts to induce fatal infectious illnesses among enemy combatants is hardly a recent concept and actually dates back in time to an era long before the acceptance of the germ theory of disease. The first documented intentional use of biological agents as weapons of warfare occurred no later than the Middle Ages, when attacking 14th century Tatar forces in what is now Ukraine catapulted the corpses of their troops who had succumbed plague into a besieged stronghold in an attempt to induce an outbreak of plague among their enemy.[1] Other evidence of such intentional use of a biological agent as a weapon can be found in North America during the mid 18th century, when British commander Sir Jeffrey Amherst ordered the transfer of blankets used by British smallpox victims to Native American tribal members, ostensibly as a gesture of goodwill, with the intention of inducing illness.[1] Indeed, the United States had a program of developing biological agents for use in warfare well into the Vietnam War era until that strategy was abandoned and the offensive use of such weapons countermanded by US policy under executive orders of President Richard Nixon in 1969-1970.[1]

International Threats

Since the Persian Gulf conflict of the early 1990s, attention has focused on the arsenals of biological warfare agents amassed by Iraq and by the nations comprising the former Soviet Union. During the Cold War era, Soviet military experts oversaw the weaponization of a variety of bacteria and viruses; unfortunately, the whereabouts of much of this material is currently unknown.[2] Also in the 1990s, Japan's quasi-religious Aum Shinrykyo cult planned attacks using biologic agents, specifically anthrax and botulinum toxin.[3] While these biological attacks were unsuccessful, cult members later implemented the release of sarin nerve gas in the Tokyo sub-

way system, killing 12 persons, affecting almost 1000 persons, and inducing panic in the population.[4]

Incidents and Hoaxes in the United States

The United States has not escaped such assaults, as biological agent attacks against American citizens have already occurred, and plans for others were discovered before their successful implementation. In 1984, members of the Rajneesh cult contaminated salad bars in Oregon with salmonella organisms, resulting in the infection of 751 persons.[5] Moreover, a variety of feigned exposures to anthrax spores occurred in several US cities in 1998, including Cincinnati, Louisville, and Indianapolis.[6] In the latter city, a full-scale response by emergency services and public health personnel occurred before the episode was proven to be a hoax.

Events Since September 11, 2001

The terrorist attacks of September 11, 2001, immediately led to active discussions about the heightened potential for biological warfare. Within only a few days, the first case of inhalation anthrax due to intentional exposure on American soil was documented, following closely thereafter by additional cutaneous and inhalational cases associated with contaminated letters sent through the mail. The last human infection in that cluster was believed to be a fatal inhalational case in an elderly woman in Connecticut. These exposures, both actual and potential, point out the need for a high level of preparedness in this country for bioterrorist activities.

Currently, the network of local and state health departments throughout the nation, with the support of the national Centers for Disease Control and Prevention (CDC), form the backbone of the surveillance and response system for such events. A variety of other federal entities, including the Department of Defense, the Office of Emergency Preparedness, the Federal Emergency Management Agency (FEMA), the Department of Veterans Affairs, the Central Intelligence Agency (CIA), and the Federal Bureau of Investigation (FBI) are also actively involved in integrated planning efforts on the national level. Additionally, the national surveillance arm is supplemented by arrangements with 3 elements of the medical care delivery system: emergency room physicians from hospitals serving selected large metropolitan areas, the network of infectious disease physicians throughout the nation, and selected international travel clinics.

Table 1A. CDC Designated A* Bioterrorism Agents

- Variola (smallpox)
- *Bacillus anthracis* (anthrax)
- *Yersinia pestis* (plague)
- *Francisella tularensis* (tularemia)
- *Clostridium botulinum* (botulism) toxin
- Filovirus and Arenavirus (hemorrhagic fevers)

* *Categorization based on potential for aerosol transmission, susceptibility of civilian population, high morbidity and mortality rates, likelihood for delayed diagnosis, and ineffective or low-efficacy therapies.*

Why Should Primary Care Clinicians be Concerned About Bioterrorism?

The Threat of Announced and Covert Attacks

Thus, the reality and continued threat of bioterrorist actions against citizens of the United States has generated extensive plans for detection and response involving several elements of our health care system. The rationale for such planning is singularly straightforward: failure to make the earliest possible diagnosis of cases in the first wave of illness following covert exposure risks substantially greater loss of human life. However, in an era of increased penetration of managed care and emphasis on the provision of care in rural areas, persons with acute infectious diseases are less likely to directly access either infectious disease specialists or emergency rooms. Instead, many are likely to be seen first by PCPs. The process of referral of such individuals to infectious disease specialists would consume additional time, potentially resulting in many more cases or deaths before the source could be identified and contained. Moreover, in the event of a large-scale exposure, these clinicians would necessarily be called upon to support the civilian health sector response in the form of managing the determination of individual need for essential immunizations and chemoprophylaxis.

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Table 1B. Clinical Syndromes Suggestive of Bioterrorism-Associated Illness

Agent	Clinical Presentation
Anthrax	Widened mediastinum, not associated with chest trauma
Smallpox	Characteristic vesiculopustular rash, with eruption of palms and soles, involving face more than chest, and all lesions in same phase of development
Botulism	Prominent neurologic symptoms: descending paralysis beginning with cranial nerve palsies
Plague, Tularemia	Increased incidence of atypical pneumonia in population
Viral Hemorrhagic Fever	Shock syndrome with hemorrhagic diathesis

What PCPs Must Know About the Detection and Management of Bioterrorism-Associated Illness

Clearly, it is critical to involve the full spectrum of PCPs in preparation for the possibility of bioterrorist events in the following ways:

1) connecting them with a vital national surveillance network to enhance the capacity for early detection and large-scale response;
2) educating them in both medical school curricula and residency training regarding syndromes or disease patterns that would make one suspect biological warfare agent exposures as well as preferred immunobiologic and pharmaceutical management strategies.

The remainder of the article will focus upon the so-called Category A Bioterrorism Agents. These are the 6 biologicals considered most likely to be used in a terrorist event: smallpox, anthrax, botulism, tularemia, plague, and the hemorrhagic fever viruses. The likelihood of these bacteria, viruses, and biotoxins is based upon potential for aerosol transmission, susceptibility of the civilian population, the projection of high morbidity and mortality rates, likelihood for delayed diagnosis, and the availability of ineffective or low-efficacy therapies.

Smallpox

Perhaps the worst-case scenario in bioterrorism in terms of both immediate consequences and the potential for secondary and further generations of infection is exposure to smallpox. Most physicians in practice have received lectures about the disease and many will remember being immunized; however, few have had significant experience in diagnosis, and even fewer have seen even one case of illness in the past 40 years. Therefore, the potential for the failure of physicians to recognize this disease in its first wave is great, allowing the propagation of further generations of infection.

Epidemiology and Clinical Features of Smallpox

Transmission of smallpox to humans may occur via fomites, but the risk of infection is greatest when aerosolized particles enter the respiratory tract. Following an incubation period averaging 12-14 days, symptoms begin with the abrupt onset of chills, fever, malaise, vomiting, headache, backache, and occasionally mental status changes or an erythematous macular rash. After 2-3 more days, an enanthem and discrete papular rash of the face, hands and arms begin, later spreading to the legs and finally the trunk.[7] The papules evolve into vesicles and finally pustules while fever and pain persist. Most lesions develop on the face and extremities and unlike chickenpox, all are synchronous—that is, in the same phase of development at a given time. The pustules form scabs that are infectious until separation, and form deep, depigmented scars.[7]

Mortality from smallpox is 3% among vaccinated persons and 30% overall among those who are unvaccinated.[8] Among those with a secondary bacterial pneumonia, mortality rises to 50%.[9] Death usually occurs in the second week of illness, although 5-10% of cases with a more fulminant course progress to death within 7 days.

Clinical Forms of Variola

There are 2 recognized clinical categories of smallpox: Variola major and variola minor, also known as alastrim. Variola major is by far the more severe form, with a case-fatality rate of 30% or more; the fatality rate for variola minor is 1% or less.

Variola major is further subcategorized into: ordinary, modified, flat, and hemorrhagic smallpox. Ordinary smallpox is what is most commonly seen: the sudden onset of a prodromal illness with fever to 101°F or more and headache, myalgias, and malaise, followed by the slow progression of a rash, which becomes most prominent on the face and extremities. Modified smallpox occurs in persons with some degree of pre-existing immunity and presents with a less severe prodrome, no fever as the rapidly evolving rash progresses, and with a much lower mortality rate. Flat and hemorrhagic smallpox have much more severe prodromes and constitutional symptoms and present with atypical lesions; fortunately, both types are uncommon.[10]

Distinguishing Smallpox from Chickenpox

It is absolutely critical to distinguish smallpox from primary varicella, or chickenpox. The pattern of symptoms preceding the occurrence of the rash in smallpox is one of the most characteristic features in recognizing the disease. Typically, smallpox symptoms begin 1-4 days before rash onset with fever of 101°F or higher and severe prostration; ie, persons appear severely ill. On the other hand, chickenpox presents with a short, mild prodrome, minimal fever before rash onset, and mild constitutional symptoms.[10]

The rash of smallpox is described as both deep and hard, and begins as rounded, well circumscribed lesions that can umbilicate or become confluent. They mature slowly (1-2 days per stage), remaining synchronous in their maturation with all lesions in the same stage of development. The rash of smallpox has a centrifugal distribution, with the highest density of lesions on the face, greater density on the

Table 2. Agents with Risk for Secondary Transmission of Illness

Agent	Secondary Transmission Risk
Smallpox	Yes
Anthrax	No
Botulism	No
Tularemia	No
Plague	Yes
VHF	Yes, for certain agents

extremities than the trunk, and greater density on the distal compared to proximal extremities, with lesions on both palms and soles. In contrast to this pattern, the rash of chickenpox is superficial, is not well demarcated, and evolves rapidly over a 24-hour period. It makes its appearance in asynchronous waves or "crops", with lesions in all stages of maturity (vesicles, pustules, scabs) at any given time. The lesions of chickenpox are clustered much more densely over the trunk, with fewer lesions on the face and extremities, and do not appear on palms or soles.[7] In persons who received chickenpox vaccine, the rash is mild with few lesions. In the United States, chickenpox is primarily a disease of children; only about 5% of adults have not had the disease. Should laboratory assistance in the diagnosis of chickenpox be required, possible approaches include the use of a Direct Fluorescent Antibody (DFA) test, electron microscopy, or the polymerase chain reaction (PCR) for detection of varicella-zoster virus in material obtained from lesions.[10] Also to be distinguished are monkeypox, which typically causes cervical and inguinal adenopathy, and skin eruptions from exposures to certain drugs or skin contact agents, such as erythema multiforme and allergic dermatitis.[9]

The CDC has developed major and minor criteria to assist with the diagnosis of smallpox. Major criteria are defined as: 1) significant febrile prodrome 1-4 days before rash onset; fever of 101°F or higher; at least 1 additional symptom; 2) rash lesions that are deep, firm or hard, and well circumscribed; and 3) lesions in the same stage of development on any part of the body. Minor criteria for the diagnosis of smallpox are: 1) centrifugal distribution, ie, lesions concentrated on the face and distal extremities; 2) first appearance of lesions on the oral mucosa/palate, face, or forearms; 3) toxic or moribund appearance of the patient; and 4) slow evolution of lesions over several days.[10]

Based upon the above criteria, CDC has also defined 3 categories of risk that a patient may have smallpox. High-risk patients have illnesses meeting 3 or more criteria; intermediate risk patients have a febrile prodrome with 1 major and at least 4 minor criteria. Low-risk persons have experienced no febrile prodrome or have fever preceding the rash but meet 3 or fewer minor criteria. The CDC's working case definition for isolation and management purposes is an illness with the following: 1) an acute onset of fever of at least 101°F; 2) a rash with firm, deep-seated vesicles or pustules in the same stage of development; and 3) no other evident cause.[10]

Epidemiology of Smallpox

Transmission of variola occurs mainly by inhalation of aerosolized virus particles. Most cases result from direct contact or proximity of 6 feet or less to an infected person. *It is important to note that patients infected with smallpox can neither transmit virus during the incubation period nor during the first 24-48 hours of the prodrome but only as the rash itself appears*. Persons with a severe rash and presence of oral or pharyngeal lesions are more infectious than those with a minor eruption. Peak infectivity occurs during the first week of rash, but transmission may occur until all scabs separate from the skin, as live virus is present in material draining from ruptured pustules and scabs. The majority of secondary infections occur in household or hospital contacts of cases. Successful interruption of transmission requires the isolation of infected patients, the identification and vaccination of contacts, and the isolation of those contacts who develop signs of illness.

Smallpox Vaccine

Smallpox vaccine actually contains live vaccinia, an attenuated virus derived from cowpox. It is a lyophilized or freeze-dried preparation that also contains glycerin, polymyxin B, streptomycin, tetracycline, neomycin, and phenol in each 100-dose vial. The efficacy of the vaccine is about 90% among persons with a vaccination scar and gives solid immunity up to 5 years after immunization. Immunity is known to wane at 10 years or more after vaccination. Based upon studies in Europe from 1950 to 1971, the risk of dying from smallpox based upon time since vaccination is 1.3% within 10 years, 7% between 10 and 20 years, and 11% beginning at 20 years; the fatality rate is as high as 52% for those never vaccinated.[10]

At present, smallpox vaccine is indicated for only a small number of individuals, specifically laboratory or other health

Table 3. Availability of Licensed, Pre-Exposure Vaccines for Prevention of Bioterrorism Associated Disease

Agent	Vaccine
Smallpox	Yes: currently approved on as-needed basis for lab workers
Anthrax	Yes: vaccine for civilian use must be approved by Dept of Defense
Botulism	No
Tularemia	No
Plague	No
VHF	Only for yellow fever

care workers who may be exposed to native or recombinant strains of vaccinia or to other orthopox-viruses capable of infecting humans. These restricted indications are based on the eradication of smallpox virus in 1978 and the known risks of immunization. **If variola virus were to be intentionally released,** smallpox vaccine would be indicated for the following groups, according to CDC:

1) persons involved in direct medical or public health evaluation, care, or transportation of confirmed or suspected smallpox patients; 2) laboratory personnel who collect or process clinical specimens; and 3) other persons who may have contact with infectious materials. In pre-exposure situations, contraindications to vaccine use exist for persons with: a history of serious allergic reaction to a previous dose or a vaccine component; immunosuppression or household contact with an immunosuppressed person; pregnancy; and a personal history of or having a household contact with eczema. Relative contraindications to vaccine use exist for persons younger age 18 and those who are currently experiencing moderate-to-severe acute illnesses. **In the event of confirmed exposure to smallpox, however, there are no valid contraindications to use of vaccine.**[10]

Complications of Smallpox Vaccination

Severe adverse events are fortunately rare and are more common in first-time vaccines and infants. *Inadvertent inoculation* of other body sites from touching the primary vaccination site accounts for about one half of such complications. The face, eyelid, nose, mouth, genitalia, and rectum are the areas most commonly involved in auto-inoculation. Rashes may occur at around 10 days after vaccination and are usually red, flat, or urticarial but do not vesiculate; they resolve in 2-4 days and are not associated with severe illness or high fever. *Generalized vaccinia* results in vesicles or pustules distant from the vaccination site; it also usually causes only minor illness. *Eczema vaccinatum* occurs in 1 out of 25,000 primary vaccinations. It occurs in people with a history of eczema and is characterized by the generalized spread of vaccinia, resulting in potentially severe morbidity. *Progressive vaccinia* causes necrosis at the vaccine site. This severe and potentially fatal complication is fortunately rare, with an incidence of 1/600,000, occurring among persons with immune deficiencies of the T-cell type. *Post-vaccinial encephalitis* occurs most often in children younger than 1 year of age and older adults who receive their first vaccination. It likely results from a hypersensitivity or autoimmune reactions and carries a fatality rate of 15-25%; about one fourth of survivors have neurologic sequelae.[10]

Post-Exposure Management

Any person exposed to smallpox should be immunized immediately with either the calf lymph derived or the new cell culture-derived vaccine when it becomes available.[9] Vaccination against smallpox is effective in preventing death if given up to 5 days after exposure and in preventing illness if given within 72 hours. Quarantine of those exposed should continue for 17 days, as they may transmit infection asymptomatically through oral and pharyngeal secretions.[9]

Treatment of Clinical Cases

There are currently no known agents with proven efficacy against active smallpox infection in humans. Treatment of active smallpox can be attempted with cidofovir, an agent with activity against many pox viruses; 3 other agents, adefovir dipivoxide, cyclic cidofovir, and ribavirin may also be candidates for use in this setting.[9]

Anthrax

Anthrax exposure has received perhaps the greatest notoriety of all the potential agents of bioterrorism, particularly since the events of September 11, 2001, and the subsequent exposure of US citizens through intentionally contaminated mail. It is unique among the 6 agents discussed in this article in that a large-scale, point-source exposure of a population to weaponized organisms was recognized in the Soviet city of Sverdlovsk in 1979. This outbreak occurred in proximity to a biological weapons development facility following the unintentional release of aerosolized anthrax spores, resulting in 66 deaths.[1] Additionally, anthrax appears to be the favored purported agent used in the exposure hoaxes reported in cities across the nation. While the exposure of a population to anthrax spores would wreak heavy casualties, there is no potential for a second generation of illness, since anthrax cannot be transmitted from person to person. However, there could be delayed exposures if decontamination of spores does not occur promptly.

Epidemiology and Clinical Features of Infection

Infection of humans with anthrax can occur via 3 routes:

1) Cutaneous, by the inoculation of skin lesions with spores carried by infected animals, chiefly cattle, sheep, or goats. This form is rarely fatal and has not been reported in the United States since 1992.[11]

2) Gastrointestinal, by eating meat from infected animals. This exposure route is only rarely encountered.

3) Inhalation, by the deposition of spores in the respiratory tract. Naturally occurring inhalational infection, associated with exposure to hides, wool, or other animal products during processing, is known as Woolsorter's Disease and has been essentially eliminated among workers in the developed world by use of the anthrax vaccine. After inhalational exposure, the spores enter pulmonary macrophages and the mediastinal lymph nodes. After germination, the vegetative phase begins with necrosis of the nodes, followed by bacterial entry into the general circulation and ensuing fatal sepsis with generalized hemorrhage and necrosis. It is anticipated that a bioterrorist attack would attempt human infection by this route, given that the cutaneous and gastrointestinal routes of exposure are less reliable and do not lend themselves as readily to mass exposure.

Following an incubation period of 1-6 days[12] after respiratory exposure, a nonspecific prodrome of fever, malaise, myalgia,

Table 4. Treatment Regimens for Agents of Bioterrorism[9]

Variola	Treatment of active smallpox can be attempted with cidofovir, an agent with activity against many pox viruses; 3 other agents, adefovir dipivoxide, cyclic cidofovir, and ribavirin may also be candidates for use in this setting.
Anthrax	IV administration of ciprofloxacin 400 mg every 8-12 hours.
Botulism	Trivalent equine antitoxin if the disease is in a phase of progression. Contact of the CDC for release of antitoxin. Skin testing should be done first to avoid the occurrence of anaphy laxis or serum sickness.
Tularemia	Streptomycin given 1 gm IM twice daily for 10 days.
Plague	Streptomycin 30 mg/kg IM per day in 2 divided doses. (Gentamicin is considered a substitute agent). IV chloramphenicol may be given for plague meningitis or in sepsis syndrome. IV doxycycline (100 mg every 12 hours for 10-14 days, after an initial loading dose of 200 mg) is also effective
VHF	None proven to be effective. Ribavirin may be considered for use in certain circumstances.

fatigue, cough, and chest pain develops. An interval of improvement often occurs over the next 2-3 days before the final phase is introduced by high fever, dyspnea, cyanosis, followed by septic shock, hematogenous dissemination of infection, and death within 36 hours.[13,14] Hemorrhagic meningitis may occur as a manifestation of metastatic infection in up to half of the cases.[15]

The physical findings in human anthrax are rather nonspecific. Radiographically, anthrax does not usually present as a pneumonia. Rather, the chest x-ray classically will show mediastinal widening with pleural effusions, manifestations of a necrotizing hemorrhagic mediastinitis.[13-16] There are generally no pulmonary infiltrates. Clinical conditions that produce similar radiographic findings, such as blunt chest trauma or deceleration injury, especially following motor vehicle accidents, and the post-thoracic surgery state should be readily distinguishable.[17]

Findings in the First 10 Inhalational Anthrax Cases in the United States after Sept. 11, 2001

The first 10 cases of inhalational anthrax in US citizens resulting from intentional exposure were recorded from October 4 to November 2, 2001. All but one of these were traced to contact with contaminated letters or packages sent through the mail. A review of the findings in these cases by Jernigan and colleagues[18] has proven very useful for defining clinical illness due to anthrax in the modern era by elucidating the following key characteristics. The mean incubation period, or time from exposure to onset of symptoms, was 4 days. Care was sought a median of 3.5 days after appearance of symptoms. Profound, drenching sweats were a notable feature of illness not previously emphasized; the brief period of improvement between the initial and fulminant phases mentioned in earlier case reports was not recognized. All of the 4 patients with fulminant symptoms at the time of presentation for care died. The median initial white blood count was 9800 rising to median peak of 26,400. Initial chest x-rays from all patients were abnormal. While only 7/10 had mediastinal changes, all had pleural effusions and 70% of these required drainage; fluid analyses showed hemorrhagic changes with few leukocytes. CT scans of the chest showed mediastinal lymphadenopathy in 7 out of 8 persons. Blood cultures were universally positive if obtained before initiation of antibiotics and grew *B anthracis* within 12-24 hours. The overall death rate of 40% was lower than anticipated, based upon historical data; early treatment with a fluoroquinolone plus at least 1 other antibiotic active against anthrax may have lowered the mortality rate.[18]

Post-Exposure Prophylaxis

If individuals can be reached soon after exposure, the use of ciprofloxacin 500 mg orally b.i.d. or doxycycline 100 mg b.i.d. orally should be given for a period of 60 days; a modified weight-based dosing has been proposed for children.[19] Due to concerns about adverse effects of fluoroquinolones or tetracyclines in children, they should be switched to amoxicillin 80 mg/kg/d in 3 divided doses if penicillin sensitivity of organisms is confirmed. Under no circumstances should cephalosporins or trimethoprim/sulfamethoxazole be used, given the resistance of known anthrax isolates to these agents.[19] Additional options for extension of coverage with oral antibiotics for 40 days with or without 3 doses of anthrax vaccine over a 4-week period under an Investigational New Drug (IND) protocol have also been proposed by CDC, based on the possibility of late germination of spores.[20] Currently, control and distribution of the anthrax vaccine is under the direction of the Department of Defense and cannot readily be obtained by practitioners without special authorization.

Treatment of Cases

Without treatment, death is almost certain to occur, and historically only 5% of those infected by the respiratory route survived if therapy was not instituted within 48 hours after symptoms appeared.[17] Before concerns about bioterrorism surfaced, IV treatment with 2 million units of penicillin every 2 hours (24 million units per day) had been the standard of care. At the present time, CDC recommends IV administration of ciprofloxacin 400 mg every 12 hours or doxycycline 100 mg IV every 12 hours plus 1-2 additional agents (rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin) as the treatment of choice.[21] Since anthrax has not shown significant resistance to erythromycin, chloramphenicol, or gentamicin,[9] these drugs could be considered as alternative adjunctive agents.

Botulism

On a per gram basis, botulinum toxin is one of the most

Table 5. Post-Exposure Prophylaxis Against Agents of Bioterrorism[9]

Variola (smallpox) virus	Smallpox vaccine is effective in preventing death if given up to 5 days after exposure and in preventing illness if given within 72 hours.
Anthrax	Ciprofloxacin 500 mg orally b.i.d. or doxycycline 100 mg b.i.d. orally. Consider initiation of anthrax immunization. Antibiotic prophylaxis should continue for at least 60 days.
Botulism	Trivalent equine antitoxin, available from CDC
Tularemia	Doxycycline 100 mg or ciprofloxacin 500 mg orally b.i.d. for 14 days
Plague	Doxycycline 100 mg orally b.i.d. for 7 days
VHF	Ribavirin may be of value

toxic substances known. Practitioners are perhaps most familiar with botulism as a food-borne illness from instruction in microbiology and the immediate attention the occurrence of illness following consumption of commercially distributed or restaurant-prepared food generally receives. However, natural clinical illness may also follow exposure from infected wounds or ingestion of certain uncooked food products by infants.

Epidemiology and Clinical Features of Infection

Botulinum toxin causes illness in humans by binding to presynaptic nerve endings and blocking acetylcholine release, thus interrupting neurotransmission and causing weakness of muscles supplied by the affected nerves.[22] While natural intoxication most often follows ingestion, the inhalation route is expected to be the target of bioterrorists.[9] Symptoms will begin within 24-36 hours to several days of respiratory exposure depending on the magnitude of the dose,[23,24] starting with abnormalities of cranial nerve function. These manifest as ocular symptoms, with blurred and double vision as well as light-induced pain; disordered speech, as evidenced by articulation problems, hoarseness, and trouble swallowing; and a descending, symmetrical, skeletal muscle paralysis.[9]

The clinical examination of persons with botulism reveals them to be alert, awake, and oriented, with no fever or sensory findings. Involvement of the autonomic nervous system may be evidenced by orthostatic hypotension. Eyes may show disconjugate gaze, pupillary dilatation, and eyelid drooping. The gag reflex is absent. Constipation and urinary retention are common.[25] Cyanosis with advancing respiratory compromise signals severe impairment of phrenic nerve function and the need for immediate ventilatory support. Fortunately, less than 5% of cases are fatal if adequate treatment of respiratory failure is instituted very promptly.[9]

A variety of clinical conditions may be confused with botulism. Guillain Barré syndrome typically causes an ascending paralysis with notable sensory findings and elevated protein in the cerebrospinal fluid. Myasthenia gravis is usually, but not always, distinguished by a positive edrophonium (Tensilon) test, has a typical electromyographic profile, and induces antibodies to acetylcholine receptors. Additionally, the Eaton-Lambert syndrome, acute poliomyelitis, tick paralysis, diphtheria, hypermagnesemia, and mushroom or chemical intoxications all may induce similar neurologic manifestations and may be confused with botulism.[25]

Prophylactic Management

The horse serum-derived antitoxin against botulism is most effective if given immediately post-exposure, before the appearance of clinical symptoms,[23] though in clinical practice such opportunities rarely arise. A trivalent antitoxin is available from CDC and a heptavalent product developed by the US Army of as-yet undetermined efficacy in humans[23] is available as an Investigational New Drug.

Treatment of Cases

Treatment of active botulism involves the use of the equine antitoxin if the disease is in a phase of progression. For treatment of one or a small number of cases, direct contact of the CDC for release of antitoxin is most efficient. If large quantities are required, local, regional, or national stockpiles will need to be tapped. All antitoxin products are of equine origin, so skin testing should be done first to avoid the occurrence of anaphylaxis or serum sickness.

Tularemia

Named for the first recognition of clinical cases from Tulare County, Calif, tularemia is an organism understandably feared by microbiologists for its potential to cause infection of laboratory workers via aerosolization. An endemic infectious disease primarily of the rural south-central and western United States,[26] tularemia is a well-known risk for hunters and persons venturing into wilderness areas. Its ability to cause severe disease following respiratory exposure has made it a target for biological weapons developers.

Epidemiology and Clinical Features of Infection

The forms of *Francisella tularensis* infection recognized in humans include glandular/ulceroglandular/oculoglandular, pulmonary, gastrointestinal, and typhoidal. These result from direct penetration of the skin or exposure of mucous membranes with blood or tissue of infected animals or indirectly from bites of deeflies, ticks, or mosquitoes; inhalation; or ingestion of contaminated food or water. The typhoidal and pulmonary forms result primarily from aerosol exposures.[27]

After an incubation period of 2-10 days, patients present with fever, headache, myalgias, weight loss, fatigue, but no lymphadenopathy.[28-30] Chest pain, nonproductive cough, and pneumonia with pleural effusions may occur. Radiographically, such infection may result in patchy, lobar, or cavitary infiltrates; mortality in such cases that go untreated is about 35%.[28,31] Despite evident pulmonary involvement, secondary human-human transmission is unusual. High fever, meningitis,

Table 6. Major and Minor Criteria for Diagnosis of Smallpox

Major Criteria

- Significant febrile prodrome 1-4 days before rash onset; fever of 101°F or greater; at least 1 additional symptom;
- Rash lesions that are deep, firm or hard, and well circumscribed;
- Lesions in the same stage of development on any part of the body.

Minor criteria

- Centrifugal distribution, ie, lesions concentrated on the face and distal extremities;
- First appearance of lesions on the oral mucosa/palate, face, or forearms;
- Toxic or moribund appearance of the patient;
- Slow evolution of lesions over several days.

hepatitis, endocarditis, osteomyelitis, and septic shock may occur in the final stages of typhoidal tularemia.

The differential diagnosis of pulmonary tularemia should include all the atypical pneumonias, including psittacosis, Legionellosis, Q fever, mycoplasma, and *C pneumoniae* infections[27] as well as anthrax and plague. Tularemia would be expected to have a lower case-fatality rate than the latter 2 agents; suspicion for tularemia should be triggered by cases presenting 3-5 days after exposure with atypical pneumonia accompanied by pleuritis and hilar adenopathy.[26]

Treatment of Clinical Cases

Beta lactam antibiotics are notoriously ineffective in tularemia. In a contained casualty situation, the drug of choice for severe infections is streptomycin given 1 g IM twice daily; gentamicin may also be used. Either drug should be continued for 10 days. In mass casualty settings, either doxycycline 100 mg or ciprofloxacin 500 mg given orally twice daily for 14 days is preferred.[26]

Post-Exposure Prophylaxis

Prophylaxis immediately after recognized exposure may be given with doxycycline 100 mg or ciprofloxacin 500 mg b.i.d. for 14 days.[26] For long-term advance prophylaxis, a live attenuated vaccine has been available in the United States under an Investigational New Drug protocol.[32] Currently, it is recommended only for high-risk laboratory workers and not for post-exposure prophylaxis.[26]

Plague

A well-recognized risk for residents of the 4 corners region of the Southwest and contiguous areas, *Yersinia pestis* is thought of in this country primarily as a flea-borne illness and is perhaps easiest to recognize in its bubonic form. Sometimes a complication of other routes of exposure, the pneumonic form is transmissible from person to person and could result in secondary infection following a bioterrorist event.

Epidemiology and Clinical Features of Infection

Three forms of plague infection are recognized in the human host:

1) Bubonic, transmitted by the bite of infected fleas, leading to regional lymph node infection with pain, tenderness, swelling and, rarely, to meningitis;
2) Septicemia, beginning commonly with gastrointestinal symptoms, then proceeding to systemic symptoms with disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), and circulatory collapse; and
3) Pneumonic, the form following respiratory exposure and that most likely to be targeted by a bioterrorist attack.[33,34]

Following an incubation period of 2-3 days, primary respiratory infection with plague bacilli causes the rapid onset of fever, chills, malaise, myalgia, and headache and an acute pneumonia syndrome, accompanied by chest pain, dyspnea, and cough.[9] Sputum production is usually watery and blood-tinged but may be frankly bloody.[35] There follows a rapid progression to respiratory failure and shock.

The chest x-ray of pneumonic plague victims shows patchy or consolidated airspace disease with involvement of a single lobe or multiple lobes on both sides of the chest; cavitation of the pneumonia may be evident early on in the course of disease.[35]

Treatment of Clinical Cases

Pneumonic plague is fatal if not treated in the first 24 hours. Appropriate antibiotic therapy includes streptomycin 30 mg/kg IM per day in 2 divided doses or gentamicin IV for 10 days. IV chloramphenicol may be given for plague meningitis or in sepsis syndrome. IV doxycycline (100 mg every 12 hours for 10-14 days, after an initial loading dose of 200 mg) is also effective.[9]

Post-Exposure Prophylaxis

Unfortunately, there is no proven benefit of the plague vaccine against pneumonic infection.[36] Exposed individuals should be treated prophylactically with 100 mg of doxycycline orally every 12 hours for 7 days.[9]

Viral Hemorrhagic Fevers

The viral hemorrhagic fevers are a diverse group of febrile illnesses caused by RNA viruses. Each may be complicated by bleeding, hemorrhage, and shock. The primary groups of VHF viruses include:

Filoviruses: such as Marburg and Ebola; Arenaviruses: including Lassa fever, Argentine Hemorrhagic Fever, and Bolivian Hemorrhagic Fever; Bunyaviruses: Hanta virus, Congo-Crimean Hemorrhagic Fever, Rift Valley Fever; and Flaviviruses: yellow fever and dengue fever.

While specific insect vectors are capable of transmitting some of these viruses such as yellow fever and dengue, person to person transmission of the VHF agents via contact with blood or body fluids is primary for others like Ebola and Lassa. Bioterrorists would likely consider aerosol exposure of a population. The primary target organ of all of these viruses is the

Table 7. Distinguishing Smallpox from Chickenpox

Smallpox

- Severe prodrome with fever of 101°F or greater, with additional constitutional symptoms lasting 1-4 days*
- Lesions are deep, hard and well demarcated
- Lesions evolve slowly; each stage lasts 1-2 days
- Synchronous lesions: all in the same phase of development
- Distribution mainly on the face and distal extremities, including palms and soles

Chickenpox

- Mild prodrome with little or no fever
- Lesions are superficial and not well demarcated
- Lesions evolve quickly in less than 24 hours
- Asynchronous lesions: appear in crops waves; all phases of eruption evident over skin surface
- Distribution mainly centrally over the chest and trunk; sparing of palms and soles

***Note:** One of the most helpful clinical features in distinguishing smallpox from other viral exanthems is the presence of fever prior to onset of rash.*

vascular bed. Infection results in increased vascular permeability with petechiae, hemorrhage, and shock. Diagnosis of any of these agents may rely on serology or a variety of specific virologic techniques. Treatment of each infection is supportive, although ribavirin therapy is being evaluated as a potential alternative for certain agents and may prove useful in selected cases.[9] The only licensed product in the United States available against any of these agents is yellow fever vaccine.

Conclusion

A bioterrorist attack against Americans could result in morbidity and mortality on a scale unknown to this nation since the influenza pandemic of 1918-1919. The inclusion of PCPs as first responders in strategic planning for the defense against bioterrorism could be among the most cost effective interventions available in health care in the event of a large-scale biological agent attack. It is imperative that the nation's professional organizations, academic health centers, and governmental agencies work together to assure the appropriate education of PCPs at all levels of training to reduce the likelihood of catastrophic consequences of such an event.

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Physician CME Questions

40. Smallpox is characterized by:
    a. lesions, which are all synchronous, ie, in the same phase of development.
    b. a mortality rate of about 3% in unvaccinated persons.
    c. lesions involving the chest more than the face.
    d. absence of lesions on palms and soles.

41. For which of the following exposures is doxycycline *not* a preferred prophylactic antibiotic?
    a. Botulism
    b. Tularemia
    c. Plague
    d. Anthrax

42. The first clinical manifestation associated with botulism is usually:
    a. cranial nerve dysfunction.
    b. loss of sensation in the upper extremities.
    c. urinary retention.
    d. ascending skeletal muscle paralysis.

43. The potential for devastating results of exposure to which of the following agents has been demonstrated by an unintentional release from a biological weapons facility?
    a. Anthrax
    b. Botulism
    c. Smallpox
    d. Plague

44. A widened mediastinum is highly suggestive of respiratory exposure to which of the following?
    a. Anthrax
    b. Tularemia
    c. Plague
    d. Brucellosis

45. In the absence of a recognized release of variola virus, which of the following groups of individuals should be considered for immunization with smallpox vaccine?
    a. Lab workers in contact with native or recombinant vaccinia or other orthopoxviruses (such as monkeypox)
    b. Travelers to central Africa
    c. Police, fire, and EMS personnel
    d. All persons concerned about their risk for smallpox

46. Complications that may result from smallpox vaccination include:
    a. generalized vaccinia.
    b. eczema vaccinatum.
    c. progressive vaccinia.
    d. postvaccinial encephalitis.
    e. All of the above

47. Immunization is the most effective manner of preventing which of the following diseases following a recognized exposure?
    a. Smallpox
    b. Plague
    c. Brucellosis
    d. Tularemia

In Future Issues:

Cancer Screening for Primary Care Physicians—Roger J. Zoorob, MD